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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/083,565	02/27/2002	Chin-Wen Chi	ST99039 US CIP 1	5910

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ROSS J. OEHLER
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 12/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/083,565	CHI ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *APDR 09/18/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-9 and 12-22* is/are pending in the application.

4a) Of the above claim(s) *13-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-9,12 and 16-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. Prosecution on the merits of this application is reopened on claims 7-9, 12 and 16-22 considered unpatentable for the reasons indicated below. Accordingly, the finality of the previous Office action is hereby withdrawn.

Claims 13-15 are also pending, but have been withdrawn from further consideration by the examiner.

Drawings

2. Drawings filed 02/27/02 are acceptable.

Specification

3. "Figure 2" in the third line of the "BRIEF DESCRIPTION OF THE DRAWINGS" should be corrected as "Figure 2 (i)-(iii)" to clearly describe the drawings filed 02/27/02.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 7-9, 12 and 16-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing human hepatocellular carcinoma

cells growth and inducing apoptosis in vitro, does not reasonably provide enablement for " a method of treating hepatocelluar carcinoma..." in a patient or human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The claims are drawn to a method of treating hepatocellular carcinoma, comprising administering intravenously to a patient, particularly human, docetaxel in an amount sufficient to treat said hepatocellular carcinoma.

It is known that hepatocellular carcinomas (HCC), cholangiocarcinomas and gallbladder cancers are primary hepatobiliary malignancies which is the most common form of solid-organ cancers.

At the time of the invention was made, many groups have attempted to treat HCC with local or systemic therapies prior to attempts at surgical resection or after surgical treatment, but

have discovered that neither doxorubicin or other chemotherapeutics such as paclitaxel has been shown to have any survival benefit against HCC in clinical setting.

Docetaxel which is a new taxoid structurally similar to paclitaxel, a semisynthetic product of a renewable resource, the needles of the European yes, Taxus baccata L, has shown an active effect against cancers; and that docetaxel combined with other chemotherapeutic drugs has higher anticancer efficacy and reduced side effects in patients with breast, pancreatic, gastric urothelial carcinomas.

Geng et al. (World J Gastroenterol. 2003, 9(4):696-700), which is the post filing date of the instant invention, discloses the activity of docetaxel in reducing human hepatocellular carcinoma cell growth and inducing apoptosis in vitro, and suggests that docetaxel may be effective in the treatment of HCC. However, the Geng et al. concludes that further study in vivo and clinical research in hepatocelluar carcinoma is needed to the clinical application of docetaxel in patients with HCC.

The instant specification provides assays (see pages 6-11) to test the compounds in vitro and discloses that docetaxel exhibits human hepatocellular carcinoma cells growth inhibitory effect and induces apoptosis. However, there is no demonstrated correlation that the test and result apply to treatment of the condition embraced by the instant claim. Ex parte Maas, 9 USPQ2d 1746, makes clear "First, although appellants' specification describes certain in vitro experiments, there is no correlation on this record between in vitro experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those

studies as constituting recognized screening procedures with clear relevance to utility in humans or animals".

In vitro sensitivity to an agent does not assure in vivo response (especially in cancer art) because of a variety of host factors. It may not be possible to replicate in vivo the concentration of the agent that evoked a response in vitro. In vivo, the drug may be poorly absorbed after administration, resulting in inadequate dosing. Poor vascularization to the tumor or pharmacological sanctuaries, such as the blood-brain barrier, may result in inadequate delivery of the drug to the tumor. Detoxification of the drug in body cannot be predicted. Tumor growth in vitro may not mirror tumor growth in vivo, nor can it be established that the biopsy tissue used in the assays is truly representative of the entire tumor. Chemosensitivity assays may prove to be helpful in patients with curable disease receiving known effective first-line chemotherapy if they can demonstrate excellent predictability, slowing for the identification of the rare patient with primary resistance. However, there is no convincing evidence that this type of chemosensitivity assay exits at present.

For instance, Nakada et al. (2004) conducted a case series to study the sensitivity of ovarian cancer to cisplantin, whether an assay could reflect the actual tumor response to chemotherapy and to investigate tumor changes that were indicative of apoptosis. During this study, a histoculture drug response assay (HDRA) was used to study tissue sample response rates. One hundred and seventy-three patients with ovarian cancer participated in the study, and from this group 164 tumors were evaluated by the assay. Nine specimens weren't able to being evaluated due to color and bacterial contamination. The tumors response rate was reported as true-positive: 90%; true-negative: 78.9% and overall accuracy of 82.8%. The researchers

concluded that the high-positive rate may indicate that this assay could be used to choose appropriate drugs; however, prospective studies in larger population are necessary to establish whether this chemosensitivity test can improve the prognosis of ovarian cancer (Nakada et al., Int J Gynecol Cancer, 2005, 15(3):445-52).

As discussed, since the efficacy of said docetaxel in treating hepatocelluar carcinoma mentioned above cannot be predicted from the instant in vitro assay (or a prior art) but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 further limits the hepatocellular carcinoma as “a fibrolamellar variant”. “a fibrolamellar variant” is a histological characteristic of heptatocellular carcinoma and is not interchangeable with “a fibrolamellar variant of hepatocellular carcinomas” or “hepatocellular carcinomas with fibrolamellar variant”. Claim 8 leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 7-9, 12 and 16-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vogel et al. (The Oncologist, Feb, 1999: 4:17-33) in view of Snoeck (WO 99/13871) and McCormick (US 5972706).

The claims are drawn to a method of treating hepatocellular carcinoma, comprising administering intravenously to a patient docetaxel in an amount sufficient to treat said hepatocellular carcinoma. Further limitations include "a fibrolamellar variant" (claim 8); "a mixed hepatocellular cholangiocarcionma" (claim 9); "intravenous infusion" (claim 12); "a patient is a human" (claim 16); "docetaxel in at least one dose of from 50 to 150 mg/m^2" (claim 17); "docetaxel in at least one dose of from 60 to 100 mg/m^2" (claim 18); "docetaxel in at least one dose of 100 mg/m^2" (claim 19); "said method comprises weekly administration until the desired therapeutic effect is obtained" (claim 20); "said method comprises administration every three weeks until the desired therapeutic effect is obtained" (claim 21); and "said method comprises intravenously infusing docetaxel at a dose of 100 mg/m2 over 1 hour every three weeks until the desired therapeutic effect is obtained (claim 22).

Vogel teaches the use of docetaxel as the most effective drugs in patients with liver metastases (page 21, column 2, para. 2 thru page 23, column 1, para. 2, particularly page 22, column 2, para. 2 thru page 23, para. 1 including Table 7). Vogel also teaches the administration of 100 mg/m^2 dose of doecetaxel every three weeks by 1-h intravenous infusion (page 21, column 2, para. 4 and Table 7).

Snoeck (page 20, lines 2-3) and McCormick (column 17, lines 21-23) are being supplied as a supplemental reference to demonstrate the state art knowledge in using pharmacological agent(s) in the treatment of hepatocelluar carcinoma and liver metastases.

The teaching of Vogel differs from the claimed invention in the use of docetaxel in the treatment of hepatocelluar carcinoma (malignant tumor of the liver). To incorporate such teaching into the teaching of Vogel, would have been obvious in view of Snoeck and

McCormick who teaches the treatment of hepatocelluar carcinoma as obvious variant to the treatment of liver metastases.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the treatment of "a fibrolamellar variant" (claim 8), since the fibrolamellar variant is a histological characteristic of hepatocellular carcinoma, one having ordinary skilled in the art would have expected that the "fibrolamellar variant" of hepatocellular carcinoma would have been characteristic of the modified prior art method (Vogel, Snoeck and McCormick). Thus, the references in combination make obvious the instant invention.

With respect to the treatment of "a mixed hepatocellular cholangiocarcinoma" (claim 9), since the docetaxel is administered to the same patient population, "a patient", as disclosed in the prior art method, the claimed therapeutic utility in treating mixed hepatocellular cholangiocarcinoma would have been expected feature of the prior art. Thus, the reference(s) alone or in combination make(s) obvious the instant invention.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
Primary Patent Examiner
AU 1614

Bruce M. Kisliuk, Director
Technology Center 1600